PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Commissioner
US Department of Commerce
United States Patent and Trademark
Office, PCT
2011 South Clark Place Room
CP2/5C24
Arlington, VA 22202
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 09 May 2001 (09.05.01)	
International application No. PCT/SE00/01683	**Applicant's or agent's file reference** PCT 51590 sb
International filing date (day/month/year) 01 September 2000 (01.09.00)	**Priority date** (day/month/year) 01 September 1999 (01.09.99)
Applicant BENSE, László	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

01 March 2001 (01.03.01)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer

Claudio Borton

Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

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REC'D 27 NOV 2001
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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

10

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
PCT 51590 sb		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/SE00/01683	01.09.2000	01.09.1999
International Patent Classification (IPC) or national classification and IPC7		
A 61 K 31/465		
Applicant		
Bense, László		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 3 sheets, including this cover sheet.

☒ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of 2 sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
01.03.2001	15.11.2001
Name and mailing address of the IPEA/SE	Authorized officer
Patent- och registreringsverket Box 5055 S-102 42 STOCKHOLM Facsimile No. 08-667 72 88	Telex 17978 PATOREG-S Göran Karlsson/BS Telephone No. 08-782 25 00

Form PCT/IPEA/409 (cover sheet) (January 1998)

INTERNATIONAL PRELI[redacted]ARY EXAMINATION REPORT

International application No.
PC[redacted]SE00/01683

I. Basis of the report

1. With regard to the **elements** of the international application:*

☐ the international application as originally filed

☒ the description:

pages 1-7 , as originally filed

pages _____ , filed with the demand

pages _____ , filed with the letter of _____

☒ the claims:

pages _____ , as originally filed

pages _____ , as amended (together with any statement) under article 19

pages _____ , filed with the demand

pages 8-9 , filed with the letter of 16.10.2001

☐ the drawings:

pages _____ , as originally filed

pages _____ , filed with the demand

pages _____ , filed with the letter of _____

☐ the sequence listing part of the description:

pages _____ , as originally filed

pages _____ , filed with the demand

pages _____ , filed with the letter of _____

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language _____ which is:

☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).

☐ the language of publication of the international application (under Rule 48.3(b)).

☐ the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

☐ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages _____

☐ the claims, Nos. _____

☐ the drawings, sheet/fig _____

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2 (c)).**

* *Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).*

** *Any replacement sheet containing such amendments must be referred to under item I and annexed to this report.*

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/SE00/01683

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1-11	YES
	Claims		NO
Inventive step (IS)	Claims	1-11	YES
	Claims		NO
Industrial applicability (IA)	Claims	1-11	YES
	Claims		NO

2. Citations and explanations (Rule 70.7)

The invention relates to the use of a sustance including nicotine, nicotine derivative, intermediate metabolites of nicotine or degradation products of nicotine for the manufacture of a medicament for the purpose of counteracting obstructive lung diseases in a prophylactic or therapeutic manner.

WO, A, 9834615 discloses the use of nicotine for treatment of asthma, see especially example 8 and page 26 line 33 - page 27 line 2.

According to the applicant, asthma is not an obstructive lung disease.

Therefore, claims 1-11 of 16-10-2001 are considered to fulfil the requirements of novelty, inventive step and industrial applicability.

Claims

1. Use of a substance including nicotine, nicotine derivative, intermediate metabolites of nicotine or degradation products of nicotine for the manufacture of a medicament to be supplied to an individual of a human being or an animal for the purpose of counteracting obstructive lung diseases in a prophylactic or therapeutic manner.

2. Use according to claim 1, wherein the medicament is supplied via the blood path.

3. Use according to claim 2, wherein the medicament is intended to be administered via the gastrointestinal tract.

4. Use according to claim 2, wherein the medicament is intended to be administered transdermally.

5. Use according to claim 2, wherein the medicament is intended to be administered intravascularly.

6. Use according to claim 2, wherein the medicament is intended to be administered intranasally.

7. Use according to claim 2, wherein the medicament is intended to be administered intravaginally.

8. Use according to any one of the preceding claims, wherein said purpose is to counteract pulmonary emphysema.

9. Use according to any one of the preceding claims, wherein said nicotine-based substance includes substantially pure nicotine.

10. Use according to any one of the preceding claims, wherein said substance is absorbed by a binding agent.

11. Use according to any one of the preceding claims, wherein said individual has a congenital bilateral bronchial anomaly.

12. A method for prophylactic or therapeutic treatment of obstructive lung diseases of in individual of a human being or an animal, wherein said individual is supplied with a substance including nicotine, nicotine derivative, intermediate metabolites of nicotine or degradation products of nicotine.

13. A method according to claim 12, wherein the medicament is supplied via the blood path.

14. A method according to claim 13, wherein the medicament is intended to be administered via the gastrointestinal tract.

15. A method according to claim 13, wherein the medicament is intended to be administered transdermally.

16. A method according to claim 13, wherein the medicament is intended to be administered intravascularly.

17. A method according to claim 13, wherein the medicament is intended to be administered intranasally.

18. A method according to claim 13, wherein the medicament is intended to be administered intravaginally.

19. A method according to any one of claims 12 to 18, wherein said individual has a congenital bilateral bronchial anomaly.

RECORD COPY

PCT

REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

For receiving Office use only

International Application No. PCT/SE 00 / 0 1 6 8 3

International Filing Date 01 -09- 2000

The Swedish Patent Office
PCT International Application

Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference *(if desired) (12 characters maximum)* PCT 51590 sb

Box No. I TITLE OF INVENTION "Use of at least one substance based on nicotine and/or a substance produced from said one substance for the manufacture of a medicament, and a method for the treatment of obstructive lung diseases"

Box No. II APPLICANT

Name and address: *(Family name followed by given name: for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

BENSE, László
Postängsvägen 232
SE-145 52 Norsborg
SWEDEN

[X] This person is also inventor.

Telephone No.

Facsimile No.

Teleprinter No.

State *(that is, country)* of nationality: Sweden

State *(that is, country)* of residence: Sweden

This person is applicant for the purposes of: [X] all designated States [ ] all designated States except the United States of America [ ] the United States of America only [ ] the States indicated in the Supplemental Box

Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

Name and address: *(Family name followed by given name: for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

This person is:

[ ] applicant only

[ ] applicant and inventor

[ ] inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality:

State *(that is, country)* of residence:

This person is applicant for the purposes of: [ ] all designated States [ ] all designated States except the United States of America [ ] the United States of America only [ ] the States indicated in the Supplemental Box

[ ] Further applicants and/or (further) inventors are indicated on a continuation sheet.

Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The person identified below ~~is hereby~~/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as: [X] agent [ ] common representative

Name and address: *(Family name followed by given name: for a legal entity, full official designation. The address must include postal code and name of country.)*

BJERKÉNS PATENTBYRÅ KB, represented by
BERGLUND, Stefan; ISRAELSSON, Stefan;
BJERKÉN, Håkan or OLSSON, Jan

Östermalmsgatan 58
SE-114 50 Stockholm, SWEDEN

Telephone No. 08 - 662 08 70

Facsimile No. 08 - 663 02 60

Teleprinter No.

[ ] **Address for correspondence:** Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Box No.V DESIGNATION OF STATES

The following designations are hereby made under Rule 4.9(a) *(mark the applicable check-boxes; at least one must be marked)*:

Regional Patent

- ☒ **AP** **ARIPO Patent:** GH Ghana, GM Gambia, KE Kenya, LS Lesotho, MW Malawi, MZ Mozambique, SD Sudan, SL Sierra Leone, SZ Swaziland, TZ United Republic of Tanzania, UG Uganda, ZW Zimbabwe, and any other State which is a Contracting State of the Harare Protocol and of the PCT
- ☒ **EA** **Eurasian Patent:** AM Armenia, AZ Azerbaijan, BY Belarus, KG Kyrgyzstan, KZ Kazakhstan, MD Republic of Moldova, RU Russian Federation, TJ Tajikistan, TM Turkmenistan, and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT
- ☒ **EP** **European Patent:** AT Austria, BE Belgium, CH and LI Switzerland and Liechtenstein, CY Cyprus, DE Germany, DK Denmark, ES Spain, FI Finland, FR France, GB United Kingdom, GR Greece, IE Ireland, IT Italy, LU Luxembourg, MC Monaco, NL Netherlands, PT Portugal, SE Sweden, and any other State which is a Contracting State of the European Patent Convention and of the PCT
- ☒ **OA** **OAPI Patent:** BF Burkina Faso, BJ Benin, CF Central African Republic, CG Congo, CI Côte d'Ivoire, CM Cameroon, GA Gabon, GN Guinea, GW Guinea-Bissau, ML Mali, MR Mauritania, NE Niger, SN Senegal, TD Chad, TG Togo, and any other State which is a member State of OAPI and a Contracting State of the PCT *(if other kind of protection or treatment desired, specify on dotted line)* .....

National Patent *(if other kind of protection or treatment desired, specify on dotted line)*:

- ☒ **AE** United Arab Emirates
- ☒ **AG** Antigua and Barbuda
- ☒ **AL** Albania .....
- ☒ **AM** Armenia .....
- ☒ **AT** Austria .....
- ☒ **AU** Australia .....
- ☒ **AZ** Azerbaijan
- ☒ **BA** Bosnia and Herzegovina .....
- ☒ **BB** Barbados
- ☒ **BG** Bulgaria .....
- ☒ **BR** Brazil .....
- ☒ **BY** Belarus .....
- ☒ **BZ** Belize
- ☒ **CA** Canada
- ☒ **CH** and **LI** Switzerland and Liechtenstein
- ☒ **CN** China .....
- ☒ **CR** Costa Rica .....
- ☒ **CU** Cuba .....
- ☒ **CZ** Czech Republic and utility model
- ☒ **DE** Germany and utility model
- ☒ **DK** Denmark and utility model
- ☒ **DM** Dominica
- ☒ **DZ** Algeria .....
- ☒ **EE** Estonia and utility model
- ☒ **ES** Spain .....
- ☒ **FI** Finland and utility model
- ☒ **GB** United Kingdom
- ☒ **GD** Grenada
- ☒ **GE** Georgia .....
- ☒ **GH** Ghana .....
- ☒ **GM** Gambia
- ☒ **HR** Croatia .....
- ☒ **HU** Hungary .....
- ☒ **ID** Indonesia
- ☒ **IL** Israel .....
- ☒ **IN** India .....
- ☒ **IS** Iceland
- ☒ **JP** Japan .....
- ☒ **KE** Kenya .....
- ☒ **KG** Kyrgyzstan .....
- ☒ **KP** Democratic People's Republic of Korea .....
- ☒ **KR** Republic of Korea .....
- ☒ **KZ** Kazakhstan .....
- ☒ **LC** Saint Lucia
- ☒ **LK** Sri Lanka
- ☒ **LR** Liberia
- ☒ **LS** Lesotho .....
- ☒ **LT** Lithuania
- ☒ **LU** Luxembourg
- ☒ **LV** Latvia
- ☒ **MA** Morocco .....
- ☒ **MD** Republic of Moldova .....
- ☒ **MG** Madagascar .....
- ☒ **MK** The former Yugoslav Republic of Macedonia .....
- ☒ **MN** Mongolia
- ☒ **MW** Malawi .....
- ☒ **MX** Mexico .....
- ☒ **MZ** Mozambique
- ☒ **NO** Norway
- ☒ **NZ** New Zealand .....
- ☒ **PL** Poland .....
- ☒ **PT** Portugal .....
- ☒ **RO** Romania
- ☒ **RU** Russian Federation .....
- ☒ **SD** Sudan
- ☒ **SE** Sweden
- ☒ **SG** Singapore
- ☒ **SI** Slovenia .....
- ☒ **SK** Slovakia and utility model
- ☒ **SL** Sierra Leone .....
- ☒ **TJ** Tajikistan .....
- ☒ **TM** Turkmenistan .....
- ☒ **TR** Turkey .....
- ☒ **TT** Trinidad and Tobago .....
- ☒ **TZ** United Republic of Tanzania
- ☒ **UA** Ukraine .....
- ☒ **UG** Uganda .....
- ☒ **US** United States of America .....
- ☒ **UZ** Uzbekistan .....
- ☒ **VN** Viet Nam .....
- ☒ **YU** Yugoslavia .....
- ☒ **ZA** South Africa .....
- ☒ **ZW** Zimbabwe .....

Check-box reserved for designating States which have become party to the PCT after issuance of this sheet:

☐ .....

Precautionary Designation Statement: In addition to the designations made above, the applicant also makes under Rule 4.9(b) all other designations which would be permitted under the PCT except any designation(s) indicated in the Supplemental Box as being excluded from the scope of this statement. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit. *(Confirmation (including fees) must reach the receiving Office within the 15-month time limit.)*

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Box No. VI PRIORITY CLAIM ☐ Further priority claim indicated in the Supplemental Box.

Filing date of earlier application (day/month/year)	Number of earlier application	Where earlier application is: national application: country	regional application:* regional Office	international application: receiving Office
item (1) 01 Sept 99 01/09/99	9903085-0	Sweden		
item (2) 27 March 00 27/03/00	0001075-1	Sweden		
item (3)				

☒ The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) *(only if the earlier application was filed with the Office which for the purposes of the present international application is the receiving Office)* identified above as item(s): (1), (2)

* *Where the earlier application is an ARIPO application, it is mandatory to indicate in the Supplemental Box at least one country party to the Paris Convention for the Protection of Industrial Property for which that earlier application was filed (Rule 4.10(b)(ii)). See Supplemental Box.*

Box No. VII INTERNATIONAL SEARCHING AUTHORITY

Choice of International Searching Authority (ISA) *(if two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used):*
ISA / SE

Request to use results of earlier search; reference to that search *(if an earlier search has been carried out by or requested from the International Searching Authority):*
Date *(day/month/year)* Number Country *(or regional Office)*

Box No. VIII CHECK LIST; LANGUAGE OF FILING

This international application contains the following **number of sheets**:

request	:	3 ✓
description (excluding sequence listing part)	:	7 ✓
claims	:	2 ✓
abstract	:	1 ✓
drawings	:	
sequence listing part of description	:	
Total number of sheets	:	13 ✓

This international application is **accompanied by** the item(s) marked below:

1. ☒ fee calculation sheet
2. ☐ separate signed power of attorney
3. ☐ copy of general power of attorney; reference number, if any:
4. ☐ statement explaining lack of signature
5. ☐ priority document(s) identified in Box No. VI as item(s):
6. ☐ translation of international application into (language):
7. ☐ separate indications concerning deposited microorganism or other biological material
8. ☐ nucleotide and/or amino acid sequence listing in computer readable form
9. ☐ other *(specify)*:

Figure of the drawings which should accompany the abstract:

Language of filing of the international application: Swedish

Box No. IX SIGNATURE OF APPLICANT OR AGENT

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request).

Stockholm, August 31 2000
Bjerkéns Patentbyrå KB
Stefan Berglund

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1. Date of actual receipt of the purported international application: 01 -09- 2000
2. Drawings: ☐ received: ☒ not received:
3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application:
4. Date of timely receipt of the required corrections under PCT Article 11(2):
5. International Searching Authority (if two or more are competent): ISA / SE
6. ☐ Transmittal of search copy delayed until search fee is paid.

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Date of receipt of the record copy by the International Bureau: 25 SEPTEMBER 2000 (25.09.00)

See Notes to the request form

Användning av åtminstone ett nikotinbaserat ämne och/eller ett ur detta ämne framställt ämne för tillverkning av ett medikament samt förfarande för behandling av obstruktiva lungsjukdomar

UPPFINNINGENS BAKGRUND OCH TIDIGARE TEKNIK

Föreliggande uppfinning avser en användning av åtminstone ett nikotinbaserat ämne och/eller ett ur detta ämnen framställt ämne för tillverkning av ett medikament som skall tillföras en individ av en människa eller ett djur. Uppfinningen avser också ett förfarande för profylaktisk eller terapeutisk behandling av obstruktiva lungsjukdomar hos en individ av en människa eller ett djur.

Lungemfysem är en vanlig lungsjukdom som drabbar framförallt rökare. Sjukdomen karakteriseras av en permanent vidgning och förstöring de finaste luftrörens och lungblåsornas väggar. Lungemfysem är en mycket allvarlig sjukdom och förstörelseprocessen är irreversibel så att sjukdomen leder till en tilltagande svårighet att andas.

Lungemfysem tillhör en sjukdomsgrupp som brukar benämnas obstruktiv lungsjukdom på grund av att flödet i luftvägarna hindras av sjukdomen. Obstruktionen är den bakomliggande orsaken även till pulmonell barotrauma, inklusive spontan pneumothorax. Dessa sjukdomar har liknande symtom och lokaliserade effekter på lungvävnaden som lungemfysem.

Vid normal inandning vidgas luftrören och det motverkar obstruktionen i en viss grad. Vid den därefter följande utandningen komprimeras lungvävnaden, inklusive luftrören och en något

mindre gasvolym kan därför strömma genom luftvägarna. Det leder till en ventileffekt då en viss jämnvikt uppstår. Med ett visst övertryck i luftvägarna och lungan kan obstruktionen övervinnas och den inandade gasmängden tömmas. Trycket i lungan är emellertid inte tillräckligt för att helt tömma lungan. Det finns alltid en viss mängd luft (residualvolym; normalt hos en vuxen individ omkring 500 ml) i lungan efter det första andetaget. Denna jämnvikt beror bland annat på och påverkas av det omgivande lufttrycket; desto mer ju svagare luftvägarna är, särskilt hos för tidigt födda, omogna barn.

Vid rökning irriteras slemhinnan i luftvägarna och luftrören, vilket leder till slemhinnesvullnad. Slemhinnesvullnaden minskar luftvägarnas lumen, dvs obstruktion uppstår och därmed hindras luftflödet i luftvägarna. Detta leder till en ökning av den så kallade ventileffekten, till ett högre tryck i luftvägarna och lungan, och till en större residualvolym i lungan. Ökningen medför också en vävnadsförstörelse som ytterligare reducerar gasutbytet dvs andningsförmågan. Ifall nikotin eller nikotinliknande ämnen tillföres icke via andningen åstadkommes en kärlsammandragande, slemhinneavsvällande effekt som minskar obstruktionen.

Pulmonell barotrauma fås p.g.a. en sådan vävnadsförstörelse av det inre trycket. Pulmonell barotrauma kan i princip avse en enda alveol eller en minsta luftväg, eller flera små alveoler inom lungan. Om denna vävnadsförstörelseprocess blir utbredd i hela lungan talar vi om lungemfysem. I de fall då luften samlas diffust i själva lungvävnaden har vi ett interstitiellt emfysem eller avgränsat en bulla (blåsa). Om luften samlas intill lungsäcken avgränsat talar vi om subpleural bleb. Luften kan också komma till mellangärdet och vi har s.k. pneumomediastinum eller intill hjärtsäcken; pneumopericardium. Om vävnadsförstörelsen går så långt att lungsäcken går sönder får vi en spontan pneumothorax (SP). Med hänsyn till att patofysiologiska förändringar i lungan har dokumenterats vid SP är det icke längre relevant att kalla SP för lungsäckens sjukdom.

Obstruktionen leder till en vidgning i en lungdel och därmed till en kompression av den omkringliggande lungdelen. En sådan vidgning och kompression är irreversibel hos en rökare även om denne skulle sluta röka. Om den omkringliggande komprimerade lungdelen är mycket stor skulle kirurgi kunna komma i fråga för att avlägsna en stor blåsa av betydelse och därmed skapa utrymme för andningsarbetet. Det är emellertid ytterst sällsynt att en patient är lämpad för en sådan operation, varför väntad effekt är långt ifrån optimal.

Vävnadsförstörelsen kan vara lokaliserad till lungans övre del p.g.a. luftvägsanomali vid spontan pneumothorax eller till lungans nedre del vid alfa-1-antitrypsin (AAT)-brist. AAT är ett enzym som skyddar de elastiska fibrerna i lungan. Fibrerna är utsatta för den största belastningen i den nedre delen där lungans största vidgning äger rum när vi andas. Om den skyddande effekten upphör förloras elasticiteten och detta syns lätt på denna mest belastade vävnadsdelen.

Förstörelsen kan också bli generell utan vare sig anomali eller av AAT-brist p.g.a. rökning.

Bilateral bronkial anomali är en anatomisk medfödd obstruktion med en karaktäristiskt förändrad förgreningsstruktur av luftvägarna och denna obstruktion kan ökas med rökning. Bilateral bronkial anomali kan idag påvisas med i sig kända diagnosmetoder, exempelvis med hjälp röntgenbilder som visar den bronkiella strukturen hos en patient. Luftvägarna består av luftrör som från huvudbronken förgrenar sig till allt mindre luftrör. Det första luftröret bildar den första generationens luftrör, luftrören efter den första förgreningen kallas den andra generationens luftrör, efter den andra förgreningen den tredje generationens luftrör o.s.v. Bilateral bronkial anomali innebär att den tredje generationens luftrör saknas hos individen och är ersatta med mycket karaktäristiska, oregelbundna avsmalnande förbindelser. Luftut-

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01 -09- 2000

bytet till och särskilt från lungblåsorna kommer således att hindras av denna defekta bronkiella struktur, vilken är identifierbar.

SAMMANFATTNING AV UPPFINNINGEN

Ändamålet med föreliggande uppfinning är att tillhandahålla ett medel som motverkar sådana obstruktiva lungsjukdomar antingen profylaktiskt eller terapeutiskt.

Detta ändamål uppnås genom användande av åtminstone ett nikotinbaserat ämne och/eller ett ur detta ämne framställt ämne för tillverkning av ett medikament som skall tillföras en människa eller ett djur i syfte att profylaktiskt eller terapeutiskt motverka obstruktiva lungsjukdomar.

Sökanden har insett att nikotin, om det tillförs icke via inandning, har en hämmande effekt på utvecklingen av luftvägsobstruktion som följs av lungvävnadens irreversibla substansförlust, elasticitetsförlust och vidgning, dvs. av de negativa effekter som uppstår vid lungemfysem, pulmonell barotrauma och spontan pneumothorax. Genom att tillföra nikotin till kroppen hos personer som lider av lungemfysem är det således möjligt att hindra eller begränsa sjukdomens utveckling. Nikotin bör även ha en profylaktisk verkan, dvs. uppkomsten av lungemfysem hos personer som löper risk att få denna sjukom, exempelvis rökare som har slutat röka, kan hindras genom tillförsel av nikotin dock ej via luftrören, respiratoriska organen.

Bestämningen åtminstone ett nikotinbaserat ämne och/eller ett ur detta ämne framställt ämne skall tolkas vitt och i denna bestämning innefattas väsentligen rent nikotin, nikotinföreningar, nikotinbesläktade föreningar, nikotinderivat, intermediära metaboliter av nikotin och/eller nikotinföreningar, nedbrytningsprodukter från nikotin eller nikotinföreningar med helt eller delvis identiska, liknande effekter.

Nikotin verkar via nikotinreceptorer dels i vegetativa system och dels i musklerna. Nikotinet har på blodkärlen först en irriterande (kärlsammandragande) verkan. Blodkärlssammandragningen leder till en slemhinneavsvällning i luftvägarna, vilken motverkar obstruktionen. Om nikotin tillförs i betydligt högre doser än vad som avses med föreliggande uppfinning fås en förlamning (kärlavslappning) via de vegetativa ganglionerna och det centrala nervsystemet.

I enlighet med en utföringsform av uppfinningen skall nikotinet tillföras blodet. Det är väsentligt att nikotinet når lungorna via blodet och inte via inandningen. Den positiva effekten av nikotin på sjukdomen lungemfysem kan således inte uppnås om nikotin tillförs via tobaksrök. Det är emellertid inte uteslutet att nikotinet har en positiv effekt om det tillförs blodet direkt samtidigt som patienten röker även om den positiva effekten i detta fall kommer att reduceras.

Enligt en ytterligare utföringsform av uppfinningen kan nikotinet administreras via den gastrointestinala kanalen, transdermalt, intravasalt, intranasalt eller intravaginalt. Nikotinet kan således tillföras på en mängd olika sätt utom via luftvägarna och lungorna. Exempelvis kan nikotinet tillföras med hjälp av plåster, spray, stolpiller, piller som skall sväljas eller i form av tuggtabletter eller sugtabletter, vilket är känt i samband med rökavvänjning. Enligt ett ytterligare exempel kan nikotinet administreras med hjälp av inhalering på så sätt att det mesta av nikotinet tas upp av slemhinnorna i (gastrointestinala kanalen) munnen.

Enligt en ytterligare utföringsform av uppfinningen är nämnda nikotinbaserade ämne och/eller ur dessa ämnen framställda ämnen upptaget i ett bindemedel. Ett sådant bindemedel kan medge en långsam administrering av den aktiva nikotinsubstansen, så kallad "slow release".

Enligt en ytterligare utföringsform av uppfinningen är användningen avsedd för nämnda individ som har en medfödd bilateral bronkial anomali. Såsom nämndes inledningsvis kan förstörelsen av lungvävnaden p.g.a. rökning bli generell utan vare sig anomali eller av AAT-brist. Sökanden har emellertid kommit fram till att risken för allvarliga obstruktioner i lungorna, vilken leder till pulmonell barotrauma, såsom spontan pneumothorax och lungemfysem, är väsentligt högre för rökare som har en medfödd bilateral bronkial anomali än för rökare som inte har en sådan anomali. Denna risken torde vara i storleksordning 2000 – 3000 % högre för rökare med, än rökare utan bilateral bronkial anomali. Den bildade strukturen hos en bilateral bronkial anomali är associerad med en annorlunda funktion, såsom ventilation, perfusion, samt en hög sensibilitet för yttre faktorer såsom rökning.

Ändamålet uppnås också med ett förfarande för profylaktisk eller terapeutisk behandling av obstruktiva lungsjukdomar hos en individ av en människa eller ett djur, varvid nämnda individ tillföres ett nikotinbaserat ämne.

BESKRIVNING AV UTFÖRINGSFORMER AV UPPFINNINGEN

Det har gjorts undersökningar som visar på en inverterad korrelation mellan rökvanorna hos gravida kvinnor och risken för pulmonell barotrauma hos kvinnornas nyfödda barn. Således har nyfödda barn hos rökande kvinnor en lägre benägenhet att få pulmonell barotrauma än nyfödda barn hos kvinnor som ej röker. Undersökningar visar också att foster hos kvinnor som röker har nikotin i blodet. Detta omvända samband indikerar således att nikotin kan motverka obstruktiva lungsjukdomar.

Det är känt att utnyttja nikotin, dvs 3-(1-metyl-2-pyrrolidyl) pyridin för rökavvänjning, dvs för att minska abstinensbesvären. Den nu föreslagna användningen i enlighet med föreliggande uppfinning kan således betraktas som en andra medicinsk indi-

kation. Den ovan nämnda medicinska effekten kan uppnås hos rökare som röker, rökare som håller på att sluta att röka, rökare som har slutat att röka fram till dess sjukdomsrisken har avtagit, individer med lungobstruktion och när man önskar reducera obstruktionen i kvarvarande delar av lungorna och/eller när någon annan behandling inte är tillgänglig.

Det är naturligtvis viktigt att mängden tillfört nikotin anpassas till den individ som skall erhålla medikamentet. En lämplig dosering för att uppnå den önskade effekten kan vara 1-100mg/24h, företrädesvis 5-50mg/24h, exempelvis 7mg/24h, 14mg/24h eller 21mg/24h. Dessa doser avser ett medikament med nikotin i väsentligen ren form. En sådan dosering kan exempelvis uppnås med hjälp av tabletter av den typ som kallas "slow release". Sådana tabletter kan innehålla ett bindemedel som medger långsamt frigörande av den aktiva nikotinsubstansen. Tablet-terna är lämpligen utformade så att patienten skall ta en eller två tabletter per dygn. Doseringen kan också uppnås med ovan nämnda plåster eller med tuggtabletter som även kan innehålla smakämnen, konsistensgivare och/eller något bindemedel som har förmåga att binda nikotinet och medge att det frigörs med lämplig hastighet. Nikotinet kan föreligga i väsentligen fri form i något sådant bindemedel, vara kemiskt bundet till något ämne eller någon nikotinförening, eller såsom ett nikotinderivat.

Till skillnad från medikament för rökavvänjning eftersträvas med föreliggande uppfinning ej något snabbt nikotintillskott när patienten lider av abstinens utan snarare en långsam och över tiden jämn doseringshastighet för att uppnå en jämn plasmakoncentration och biotillgänglighet.

Uppfinningen är inte begränsad till de givna exemplen utan kan varieras och modifieras inom ramen för de efterföljande patentkraven.

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Patentkrav

1. Användning av åtminstone ett nikotinbaserat ämne och/eller ett ur detta ämne framställt ämne för tillverkning av ett medikament som skall tillföras en individ av en människa eller ett djur i syfte att profylaktiskt eller terapeutiskt motverka obstruktiva lungsjukdomar.

2. Användning enligt krav 1, varvid medikamentet tillförs via blodbanan.

3. Användning enligt krav 2, varvid medikamentet är avsett att administreras via den gastrointestinala kanalen.

4. Användning enligt krav 2, varvid medikamentet är avsett att administreras transdermalt.

5. Användning enligt krav 2, varvid medikamentet är avsett att administreras intravasalt.

6. Användning enligt krav 2, varvid medikamentet är avsett att administreras intranasalt.

7. Användning enligt krav 2, varvid medikamentet är avsett att administreras intravaginalt.

8. Användning enligt något av de föregående kraven, varvid nämnda syfte är att motverka lungemfysem.

9. Användning enligt något av de föregående kraven, varvid nämnda nikotinbaserade ämne innefattar väsentligen rent nikotin.

10. Användning enligt något av de föregående kraven, varvid nämnda nikotinbaserade ämne innefattar nikotinderivat, inter-

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mediära metaboliter av nikotin eller nedbrytningsprodukter från nikotin.

11. Användning enligt något av de föregående kraven, varvid nämnda nikotinbaserade ämne och/eller ur dessa ämnen framställda ämnen är upptaget i ett bindemedel.

12. Användning enligt något av de föregående kraven, varvid nämnda individ har en medfödd bilateral bronkial anomali.

13. Förfarande för profylaktisk eller terapeutisk behandling av obstruktiva lungsjukdomar hos en individ av en människa eller ett djur, varvid nämnda individ tillföres ett nikotinbaserat ämne.

14. Förfarande enligt krav 13, varvid medikamentet tillförs via blodbanan.

15. Förfarande enligt krav 14, varvid medikamentet är avsett att administreras via den gastrointestinala kanalen.

16. Förfarande enligt krav 14, varvid medikamentet är avsett att administreras transdermalt.

17. Förfarande enligt krav 14, varvid medikamentet är avsett att administreras intravasalt.

18. Förfarande enligt krav 14, varvid medikamentet är avsett att administreras intranasalt.

19. Förfarande enligt krav 14, varvid medikamentet är avsett att administreras intravaginalt.

20. Förfarande enligt något av kraven 13 till 19, varvid nämnda individ har en medfödd bilateral bronkial anomali.

Sammandrag

Uppfinningen avser en användning av åtminstone ett nikotinbaserat ämne och/eller ett ur detta ämne framställt ämne för tillverkning av ett medikament som skall tillföras en individ av en människa eller ett djur i syfte att profylaktiskt eller terapeutiskt motverka obstruktiva lungsjukdomar, i synnerhet lungemfysem. Medikamentet är avsett att tillföras via blodbanan och administreras via den gastrointestinala kanalen, transdermalt, intravasalt, intranasalt eller intravaginalt. Uppfinningen avser också ett förfarande för profylaktisk eller terapeutisk behandling av obstruktiva lungsjukdomar hos en individ av en människa eller ett djur, varvid nämnda individ tillföres ett nikotinbaserat ämne.

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(54) Title: USE OF AT LEAST ONE SUBSTANCE BASED ON NICOTINE AND/OR A SUBSTANCE PRODUCED FROM SAID ONE SUBSTANCE FOR THE MANUFACTURE OF A MEDICAMENT, AND A METHOD FOR TREATMENT OF OBSTRUCTIVE LUNG DISEASES

(57) Abstract: The invention refers to a use of at least one substance based on nicotine and/or a substance produced from said one substance for the manufacture of a medicament to be supplied to an individual of a human being or an animal for the purpose of counteracting, in a prophylactic or therapeutic manner, obstructive lung diseases, in particular pulmonary emphysema. The medicament is intended to be supplied via the blood path and to be administered via the gastrointestinal tract, transdermally, intravascularly, intranasally or intravaginally. The invention also refers to a method for prophylactic or therapeutic treatment of obstructive lung diseases of an individual of a human being or an animal, wherein said individual is supplied with a nicotine-based substance.

Use of at least one substance based on nicotine and/or a substance produced from said one substance for the manufacture of a medicament, and a method for treatment of obstructive lung diseases

THE BACKGROUND OF THE INVENTION AND PRIOR ART

The present invention refers to a use of at least one substance based on nicotine and/or a substance produced from said one substance for the manufacture of a medicament to be supplied to an individual of a human being or an animal. The invention also refers to a method for prophylactic or therapeutic treatment of obstructive lung diseases of in individual of a human being or an animal.

Pulmonary emphysema is a common disease, which in particular affects smokers. The disease is characterised by a permanent expansion and destruction of the finest bronchi and the walls of the alveoli. Pulmonary emphysema is a very serious disease and the destruction process is irreversible so that the disease leads to increasing respiratory difficulties.

Pulmonary emphysema belongs to a group of diseases usually called obstructive lung diseases due to the fact that the disease obstructs the flow in the respiratory tracts. The obstruction is the underlying cause also to pulmonary barotrauma, including spontaneous pneumothorax. These diseases have symptoms and localised effects to the lung tissue similar to pulmonary emphysema.

During normal inhalation the bronchi are expanded, which counteracts the obstruction to a certain extent. During the following exhalation the lung tissue is compressed, including the bronchi, and

a somewhat smaller gas volume may therefore flow through the respiratory tract. This leads to a valve effect when a certain balance arises. By a certain overpressure in the respiratory tracts and the lung, the obstruction may be overcome and the inhaled gas volume be emptied. The pressure in the lung is however not sufficient for completely emptying the lung. There is always a certain amount of air (residual volume; normally about 500 ml of an adult) in the lung after the first breath. This balance depends inter alia on and is influenced by the ambient air pressure; the more the weaker the respiratory tracts, especially for early born, immature children.

During smoking the mucous membrane in the respiratory tracts and bronchi is irritated, which leads to a swelling of the mucous membrane. This swelling decreases the lumen of the respiratory tracts, i.e. the obstruction arises and thus the air flow in the respiratory tracts is restrained. This leads to an increase of the so-called valve effect, to a higher pressure in the respiratory tracts and the lung, and to a larger residual volume in the lung. The increase also leads to a destruction of tissue, which further reduces the gas exchange, i.e. the breathing capacity. If nicotine or nicotine-like substances are supplied, not via the respiration, a vessel contracting, decongestant effect, which reduces the obstruction, is obtained.

Pulmonary barotrauma appears due to such a tissue destruction by the inner pressure. Pulmonary barotrauma may principally refer to one single alveolus or a smallest respiratory tract, or several small alveoli within the lung. If this tissue destruction process is expanded to the whole lung it is called pulmonary emphysema. In the cases when air is collected diffusely in the lung tissue proper, we have an interstitial emphysema or in a delimited way, a bulla (blister). If the air is collected adjacent to the pleura in a delimited manner we have a subpleural bleb. The air may also come to the intrapulmonary space and we have a so-called pneumomediastinum or into the heart sack; pneumopericardium. If the tissue destruction is expanded so that the pleura is destroyed, we have a spontaneous pneumothorax (SP). With regard to the fact that

pathophysiological changes in the lung are documented in case of SP, it is not any longer relevant to call SP a disease of the pleura.

The obstruction leads to an expansion in a lung part and thus to a compression of the surrounding lung part. Such an expansion and compression is irreversible for a smoker even if he would stop smoking. If the surrounding compressed lung part is very large, surgery could be considered for removing a large significant blister and thus create space for the respiratory work. However, it is very rare that a patient is suitable for such an operation, whereby an expected effect is far from being optimal.

The destruction of tissue may be localised to the upper part of the lung, due to bronchial anomaly at spontaneous pneumothorax or to the lower part of the lung at alfa-1-antitrypsin AAT-deficiency. AAT is an enzyme protecting the elastic fibres of the lung. The fibres are subjected to the largest load in the lower part, where the largest expansion of the lung takes place when we breathe. If the protecting effect ceases, the elasticity is lost and this can be easily seen on the most stressed tissue part.

The destruction may also be general without anomaly or AAT-deficiency due to smoking.

Bilateral bronchial anomaly is an anatomical congenital obstruction with a characteristically changed branching structure of the respiratory tracts and this obstruction may be increased by smoking. Bilateral bronchial anomaly may today be shown by diagnostic methods known per se, for instance by means of X-ray pictures disclosing the bronchial structure of a patient. The respiratory tracts consist of bronchi, which from the main bronchus are divided to smaller and smaller bronchi. The first bronchus forms the bronchus of the first generation, the bronchi after the first division are called the bronchi of the second generation, after the second division the bronchi of the third generation, etc. Bilateral bronchial anomaly means that the bronchi of the third generation are missing in an individual and are replaced by very characteristic,

irregular narrowing connections. The air exchange to and especially from the alveoli will thus be hampered by this defect bronchial structure, which is identifiable.

SUMMARY OF THE INVENTION

The object of the present invention is to provide a means, which counteracts such obstructive lung diseases in a prophylactic or therapeutic manner.

This object is obtained by the use of at least one substance based on nicotine and/or a substance produced from said one substance for the manufacture of a medicament to be supplied to an individual of a human being or an animal for the purpose of counteracting obstructive lung diseases in a prophylactic or therapeutic manner.

The applicant has realised that nicotine, if it is not supplied via the respiration, has an inhibitory effect on the development of respiratory tract obstruction followed by the irreversible substance loss, elasticity loss and expansion of the lung tissue, i.e. the negative effects arising from pulmonary emphysema, pulmonary barotrauma and spontaneous pneumothorax. By supplying nicotine to the body of the persons suffering by pulmonary emphysema, it is thus possible to prevent or delimit the development of the disease. Nicotine also ought to have a prophylactic effect, i.e. the origin of pulmonary emphysema of persons having a risk to be effected by this disease, for instance smokers, which have stopped smoking, may be prevented by the supply of nicotine, however not via the bronchi, respiratory organs.

The definition at least one substance based on nicotine and/or a substance produced from said one substance is to be given a broad interpretation and in this definition are included substantially pure nicotine, nicotine compounds, nicotine related compounds, nicotine derivatives, intermediate metabolites of nicotine and/or nicotine compounds, degradation products from nicotine or nicotine compounds with completely or partly identical, similar effects.

Nicotine acts via nicotine receptors partly in the vegetative system and partly in the muscles. The nicotine has firstly an irritating (vasoconstrictive) effect on the blood vessels. The vasoconstriction leads to a decongestion of the mucous membrane in the respiratory tracts, which counteracts the obstruction. If nicotine is supplied in significantly higher doses than intended by the present invention, a paralysis (vessel relaxion) arises via the vegetative ganglions and the central nervous system.

According to an embodiment of the invention, the nicotine is to be supplied via the blood. It is essential that the nicotine reaches the lungs via the blood and not via the respiration. The positive effect of nicotine to the disease pulmonary emphysema can thus not be obtained if nicotine is supplied via tobacco smoke. However, it is not excluded that nicotine has a positive effect if it is supplied to the blood immediately at the same time as the patient is smoking even if the positive effect in this case will be reduced.

According to a further embodiment of the invention, the nicotine may be administered via the gastrointestinal tract, transdermally, intravascularly, intranasally or intravaginally. The nicotine may thus be supplied in various manners except via the respiratory tracts and the lungs. For instance, the nicotine may be supplied by means of plasters, spray, suppository, pills to be swallowed or in the form of chewable tablets or oral tablets, which are known in connection with smoking cessation. According to a further example, the nicotine may be administered by means of inhalation in such a way that most of the nicotine is taken up by the mucous membranes in the mouth (gastrointestinal tract).

According to a further embodiment of the invention, said substance based on nicotine and/or substances produced by said one substance are absorbed in a binding agent. Such a binding agent may permit a slow administration of the active nicotine substance, so-called "slow release".

According to a further embodiment of the invention, the use is intended for said individual, which has a congenital bilateral bronchial anomaly. As mentioned initially, the destruction of the lung tissue, due to smoking, may be general without anomaly or due to AAT-deficiency. The applicant has however realised that the risk of serious obstructions in the lungs, which leads to pulmonary barotrauma, such as spontaneous pneumothorax and pulmonary emphysema, is substantially higher for smokers having a congenital bilateral bronchial anomaly than for smokers not having such an anomaly. This risk ought to be in the order of 2000-3000 % higher for smokers with, than smokers without bilateral bronchial anomaly. The formed structure of a bilateral bronchial anomaly is associated with a different function, such as ventilation, perfusion, and a high sensibility for external factors, such as smoking.

The object is also obtained by a method for prophylactic or therapeutic treatment of obstructive lung diseases of an individual of a human being or an animal, wherein said individual is supplied with a nicotine-based substance.

DESCRIPTION OF EMBODIMENTS OF THE INVENTION

Investigations have been made showing an inverted correlation between smoking habits of pregnant women and the risk of pulmonary barotrauma of the new-born children of the women. Thus, new-born children of smoking women have a lower predisposition to get pulmonary barotrauma than new-born children of women which are not smoking. Investigations also show that foetuses of women which smoke have nicotine in the blood. This inverted relation thus indicates that nicotine may counteract obstructive lung diseases.

It is known to use nicotine, i.e. 3-(1-metyl-2-pyrrolidyl) pyridine for smoking cessation, i.e. for reducing the abstinence complaints. The use now proposed according to the present invention may thus be regarded as a second medical indication. The medical effect mentioned above may be obtained for smokers which are smoking,

smokers which are giving up their smoking, smokers which have giving up their smoking until this disease risk is reduced, individuals with a lung obstruction and when one wishes to reduce the obstruction in remaining parts of the lungs and/or no other treatment is available.

It is of course important that the quantity of nicotine supplied is adapted to the individual to receive the medicament. A suitable dosing for obtaining the desired effect may be 1-100 mg/24h, preferably 5-50 mg/24h, for instance 7mg/24h, 14mg/24h or 21mg/24h. These doses refer to a medicament with nicotine in substantially pure form.

Such a dose may for instance be obtained by means of tablets of the type called "slow release". Such tablets may contain a binding agent permitting a slow release of the active nicotine substance. The tablets are suitably designed in such a way that the patient may take one or two tablets per 24h. The dose may also be obtained by the plasters mentioned above or chewable tablets which also may contain flavouring substances, consistency agents and/or any binding agent having an ability to bind nicotine and permit the release thereof at a suitable speed. The nicotine may be present in a substantially free form in such a binding agent, be chemically bounded to any substance or any nicotine compound or as a nicotine derivative.

In contrast to the medicament for smoking cessation, there is no desire of the present invention to obtain any quick addition when the patient suffers from abstinence but rather a slow and over the time uniform dosing speed in order to obtain an equal plasma concentration and bioavailability.

The invention is not limited to the examples given but may be varied and modified within the scope of the following claims.

Claims

1. Use of at least one substance based on nicotine and/or a substance produced from said one substance for the manufacture of a medicament to be supplied to an individual of a human being or an animal for the purpose of counteracting obstructive lung diseases in a prophylactic or therapeutic manner.

2. Use according to claim 1, wherein the medicament is supplied via the blood path.

3. Use according to claim 2, wherein the medicament is intended to be administered via the gastrointestinal tract.

4. Use according to claim 2, wherein the medicament is intended to be administered transdermally.

5. Use according to claim 2, wherein the medicament is intended to be administered intravascularly.

6. Use according to claim 2, wherein the medicament is intended to be administered intranasally.

7. Use according to claim 2, wherein the medicament is intended to be administered intravaginally.

8. Use according to any one of the preceding claims, wherein said purpose is to counteract pulmonary emphysema.

9. Use according to any one of the preceding claims, wherein said nicotine-based substance includes substantially pure nicotine.

10. Use according to any one of the preceding claims, wherein said nicotine-based substance includes nicotine derivative, intermediate metabolites of nicotine or degradation products of nicotine.

11. Use according to any one of the preceding claims, wherein said one substance based on nicotine and/or substances produced from said one substance are absorbed by a binding agent.

12. Use according to any one of the preceding claims, wherein said individual has a congenital bilateral bronchial anomaly.

13. A method for prophylactic or therapeutic treatment of obstructive lung diseases of in individual of a human being or an animal, wherein said individual is supplied with a nicotine-based substance.

14. A method according to claim 13, wherein the medicament is supplied via the blood path.

15. A method according to claim 14, wherein the medicament is intended to be administered via the gastrointestinal tract.

16. A method according to claim 14, wherein the medicament is intended to be administered transdermally.

17. A method according to claim 14, wherein the medicament is intended to be administered intravascularly.

18. A method according to claim 14, wherein the medicament is intended to be administered intranasally.

19. A method according to claim 14, wherein the medicament is intended to be administered intravaginally.

20. A method according to any one of claims 13 to 19, wherein said individual has a congenital bilateral bronchial anomaly.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 00/01683

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: A61K 31/465
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 9834615 A1 (SYNAPSE PHARMACEUTICALS INTERNATIONAL, INC.), 13 August 1998 (13.08.98), see page 26, line 33 - page 27, line 2 and example 8	9

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☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
15 December 2000	28 -12- 2000
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Göran Karlsson/EÖ Telephone No. +46 8 782 25 00

Form PCT/ISA/210 (second sheet) (July 1998)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE00/01683

Box I **Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 1-8 and 10-13
because they relate to subject matter not required to be searched by this Authority, namely:
see next sheet

2. ☒ Claims Nos.: 1-8, 10-13
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
A method for treatment of the human or animal body by therapy, see Rule 39.1

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II **Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

The expressions "nikotinbaserat ämne", "och/eller ett ur detta ämne framställt ämne", "nikotinderivat", "intermediära metaboliter av nikotin" och "nedbrytningsprodukter av nikotin" are not considered to be clear and concise cf. Article 6. A meaningful search of claims 1-8 and 10-13 has therefore not been possible to perform.

INTERNATIONAL SEARCH REPORT

Information on patent family members

04/12/00

International application No.
PCT/SE 00/01683

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9834615 A1	13/08/98	AU 5977598 A	26/08/98
		EP 1014981 A	05/07/00
		US 5900418 A	04/05/99
		ZA 9800960 A	17/08/98
		US 5981549 A	09/11/99
		US 5902816 A	11/05/99
		US 5824684 A	20/10/98
		US 5760049 A	02/06/98
		US 5916903 A	29/06/99